## Remarks

Claims 80, 81, 90-97 and 99 were pending in this application. By this amendment, claim 99 is canceled without prejudice. Claims 90 and 97 are amended herein to correct minor clerical errors. Support for these amendments can be found in the originally-filed claims. Applicants reserve the right to pursue at a later date any subject matter removed from consideration by this amendment.

No new matter is introduced by the foregoing amendments. After entry of this Amendment, **claims 80, 81 and 90-97 are pending in this application (of which claim 91 is currently withdrawn)**.

This amendment is proper after final rejection at least because it only cancels non-elected subject matter, corrects minor clerical errors, clarifies Applicants' position with regard to the pending rejections, and thereby places the case in better posture for an appeal if such is necessary. The amended claims do not require a new search. Consideration and allowance of the pending claims is requested.

*Restriction/Election*

Applicants note that the Office has maintained the restriction requirement of August 18, 2010 and has made it final. Claim 99 is canceled herewith without prejudice, as drawn to non-elected subject matter.

Claim 91 is currently withdrawn, being directed to non-elected species. Applicants understand that withdrawn claim 91 will be rejoined upon the allowance of generic claim 90.

*Rejection under 35 U.S.C. § 112, first paragraph (enablement)*

Claims 80, 81, 90 and 92-97 are rejected under 35 U.S.C. §112, first paragraph, for allegedly failing to comply with the enablement requirement. The Office continues to assert that the specification "lacks adequate guidance, direction or discussion to apprise the skilled artisan how the claimed compound may be used to achieve (1) the inhibition of GRP activity and (2) the

disclosed utilities for treating conditions wherein GRP inhibition has been implicated" (Office action, at page 3).

In the Amendment and Response to Non-final Office Action that was submitted May 24, 2010 (hereafter "May Response"), Applicants argued that the pending claims are sufficiently enabled in light of the nature of the invention, the knowledge in the art and the abundant guidance in the specification (including the working examples presented therein). Even in view of Applicants' references in that Response to detailed description in the specification demonstrating that the claimed compound of formula XV' (hereafter compound 77427) inhibits GRP function, the Office continues to allege "that the specification does not definitively set forth that the elected compound in fact inhibits GRP" (Office action, at page 8). The Office further asserts that because "it does not seem that the instant specification sets forth that the elected compound in fact inhibits GRP, arguments and data on how this inhibition leads to the inhibition of an activity of GRP which thereby treats different disorders or diseases is not found persuasive" (*Id.* at page 9).

Applicants traverse the maintained enablement rejection of claims 80, 81, 90 and 92-97, at least because (1) the specification clearly and unequivocally demonstrates that compound 77427 in fact inhibits GRP function and (2) having established that compound 77427 inhibits GRP function, Applicants' previously-submitted arguments and supporting references show that one of skill in the art would be able to use compound 77427 to treat a GRP-associated disease.

**Compound 77427 Inhibits GRP Function**

As discussed on page 9 of the May Response, compound 77427 was identified as a GRP inhibitor by primary and secondary screens of small molecules. The primary screen identified compounds that blocked the interaction between GRP and a GRP blocking antibody. The secondary screen tested the ability of the compounds identified in the primary screen to **affect a GRP activity in cultured cells expressing the GRP receptor**. Figure 3 of the specification presents data from this secondary screen. GRP stimulates the release of the second messenger $IP_3$ in cells expressing the GRP receptor. Figure 3A shows that in the absence of any additional compound (control), relatively little $IP_3$ release is detectable. When GRP is added to the culture media, the level of $IP_3$ released is significantly increased. In contrast, when both GRP and

compound 77427 are added to the culture media, relatively little $IP_3$ is released. These results clearly and unequivocally indicate that compound 77427 inhibits the $IP_3$-stimulating activity of GRP.

Additional evidence that compound 77427 inhibits a GRP activity is provided in Figures 5 and 6, both of which illustrate that compound 77427 inhibits the angiogenesis-stimulating activity of GRP, both *in vitro* (Figure 5) and *in vivo* (Figure 6). This data was noted on page 9 of the May Response. Figure 5 shows the effect of GRP and compound 77427 on *in vitro* endothelial cell preangiogenic cord formation. In the absence of GRP, relatively few endothelial cell cord structures are formed (top). When GRP is added, abundant endothelial cord structures are observable (middle). When GRP is added together with compound 77427, relatively few cord structures are observed (bottom). Thus, compound 77427 inhibits GRP-stimulated cord formation activity. Figure 6 shows the effects of GRP and the combination of GRP and compound 77427 on blood vessel formation in a directed *in vivo* angiogenesis assay. As shown in Figure 6, angiogenesis is stimulated in the presence of GRP. This stimulated angiogenesis is inhibited in a dose-dependent manner as the concentration of compound 77427 that is added with GRP is increased. Significantly, Figure 6 also shows that the inhibitory effects of compound 77427 on GRP-stimulated angiogenesis are similar to the effects of the known GRP inhibitor, antibody 2A11. As discussed in the May Response, antibody 2A11 has been extensively used to inhibit proliferation of multiple cancer cell types and to treat chronic lung disease in an animal model. Thus, Figure 6 not only demonstrates that compound 77427 inhibits GRP function, but also illustrates that compound 77427 inhibits GRP function in the same way as a known GRP inhibitor that has been previously used to treat GRP-stimulated disease.

The Office continues to focus on the general description of the compounds identified in the subject application as "modulating" compounds (*see* Office action, at page 8). However, Applicants reiterate that the pending claims are specifically directed to methods of "inhibiting an activity of a gastrin releasing peptide" with "a compound of formula XV'" (compound 77427). Nowhere in the specification is this specific compound referred to as a modulating compound, and nowhere in the specification is compound 77427 shown or described as able to stimulate a GRP activity. Applicants direct the Office's attention to Table 1 of the specification (pages 18-19), wherein Applicants summarize characteristics of the bioactive compounds identified in the

primary and secondary screens described above. Table 1 lists various GRP or AM stimulating (agonist) and inhibiting (antagonist) compounds, but compound 77427 is clearly labeled an antagonist of GRP-stimulated second messenger activity. Accordingly, one of skill in the art would clearly recognize that Applicants had conceived of compound 77427 as a GRP inhibitory compound at the time the application was filed.

The Office also cites the specification at page 20, line 7 (which states that "GRP-interfering small molecules by themselves did not produce any change in $IP_3$ levels") to prove that Applicants have not demonstrated that compound 77427 inhibits GRP activity. Applicants disagree with this assertion. Applicants note that the complete sentence cited in part by the Office is: "As was the case with modulators of AM, the GRP-interfering small molecules by themselves did not produce any change in $IP_3$ levels (Fig. 3A)" (page 20, lines 6-9, emphasis added). Earlier in the specification, Applicants had, in describing an analogous AM secondary screen, noted that "in the absence of AM, none of the compounds elicited any response (Fig. 2A), suggesting that the mechanism of action includes binding of the small molecule to AM rather than to the receptor" (page 18, lines 11-13). Thus, rather than prove that Applicants have not shown that compound 77427 is a GRP inhibitor, the sentence cited by the Office supports Applicants' hypothesis that the identified compounds bind to the peptide rather than the receptor.

Moreover, Applicants submit that the very nature of a secondary screen that monitors the stimulation of an activity requires the presence of the stimulant in order to observe its inhibition. Thus, it would be difficult if not impossible to detect the inhibition of GRP stimulation of $IP_3$ release by compound 77427 in the absence of GRP. As described above, the data presented in Figure 3A unequivocally shows that GRP stimulates cellular $IP_3$ levels, and addition of compound 77427 together with GRP inhibits that GRP-stimulated activity. Thus, Applicants have clearly demonstrated that compound 77427 can be used in methods of inhibiting an activity of a GRP.

**Compound 77427 Can Be Used to Treat GRP-Associated Diseases**

On pages 8-11 of the May Response, Applicants directed the Office to multiple publications that implicated GRP-stimulated activities in the etiology and progression of various diseases (including multiple types of cancer). Copies of the references were provided with the

May Response or were previously on record in this file. Several of these references also showed the use of inhibitors of GRP function to treat various diseases. Notably, several of these references employed the inhibitor of GRP function, monoclonal antibody 2A11 to inhibit the progression of various diseases (as discussed above, Applicants have shown that compound 77427 inhibits a GRP activity in an analogous manner to antibody 2A11). Applicants also directed the Office to data presented in the specification demonstrating the use of compound 77427 to inhibit disease-related GRP activities. However, in the Final Office action, the Office has refused to review these references and Applicants' arguments on the grounds that Applicants have not shown compound 77427 to inhibit GRP function. Applicants submit that the specification does clearly demonstrate that compound 77427 inhibits GRP function (see above arguments). Accordingly, Applicants respectfully request that the Office reconsider its position regarding the previously-presented arguments and data. The arguments made in the May Response are hereby incorporated herein. Applicants request withdrawal of the enablement rejection of claims 80, 81, 90 and 92-97.

*Allowable Subject Matter*

Applicants thank the Office for indicating that claims reciting use of compound 77427 to treat lung cancer are enabled and would be allowable. However, as Applicants discuss both above and in the May Response, GRP activity has been implicated in a variety of cancers and other diseases in addition to lung cancer. It follows that a compound that inhibits GRP activity (such as compound 77427) can by extension be used to treat those diseases, and claims reciting those uses are accordingly enabled and should be allowable.

*Request for Rejoinder of Withdrawn Claims*

Applicants submit that based on the foregoing arguments, one of skill in the art would be able to practice the invention described by generic claim 90 without undue experimentation. As generic claim 90 is in condition for allowance, Applicants request that the species in withdrawn claim 91 be rejoined and examined at this time.

## Request for Examiner Interview

After receiving the Final Office action of June 10, 2010, Applicants' representative Dr. Michael D. Hammer contacted the Office to schedule a telephonic interview to discuss the pending rejections with Examiner Pagonakis. Dr. Hammer did not speak with the Examiner, but left a message on her answering machine. The Examiner responded with a message on Dr. Hammer's answering machine, stating that an interview would be granted to discuss specific claim amendments, but not to discuss Applicants' position regarding the pending rejections. Applicants believe that the foregoing Amendment places the application in condition for immediate allowance, and request that this Amendment be entered, and a Notice of Allowance granted. If, in light of this Amendment, the Office maintains its position regarding the enablement of the claims, the Examiner is formally requested to contact the undersigned prior to issuance of the Advisory Action in order to arrange a telephonic interview. It is believed that a brief discussion of the merits of the present application may expedite prosecution. This request is being submitted under MPEP § 713.01, which indicates that an interview may be arranged in advance by a written request.

Respectfully submitted,

KLARQUIST SPARKMAN, LLP

One World Trade Center, Suite 1600
121 S.W. Salmon Street
Portland, Oregon 97204
Telephone: (503) 595-5300
Facsimile: (503) 595-5301

By /Michael D. Hammer/
Michael D. Hammer, Ph.D.
Registration No. 59,258